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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,705	FOEKENS ET AL.	
	Examiner	Art Unit	
	JEHANNE SITTON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *9,10 and 17-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-2010*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

DETAILED ACTION

1. Currently, claims 1-21 are pending in the instant application. Claims 9, 10, and 17-21 are withdrawn from consideration as being drawn to a non elected invention and Claims 1-8 and 11-16 are currently under examination. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are either newly applied, as necessitated by amendment, or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

Claim Rejections - 35 USC § 112 second paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 and 11-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) The claims are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps that result in the, characterization, or determining prognosis, or disease free survival, or probability of response to treatment. The claims recite only steps of obtaining a sample and determining methylation status of PITX2. The "wherein" statement in step c merely sets forth a property of the method, but does not indicate how the method accomplishes the objective of characterization, prognosis, etc by merely performing the

steps of obtaining a sample and determining methylation. There is no clear nexus between determining methylation status and determining a characterization, prognosis, etc in the claim,. Accordingly, the claims omit the essential step required by the preamble of the claims of providing a characterization, prognosis, etc.

The response asserts that a final "wherein" clause addresses the concerns raised. However it is noted that no "wherein" clause can be found in claim 1. Further, the additional subject matter in claim 1 does not provide any indication what characterization is achieved by detecting an increased methylation status.

B) Claim 1 has been amended to recite "DNA from breast cells or tissue; breast tissue; or breast cell sample". It is not clear how the second iteration of breast tissue and breast cell sample differ from the first. It is not clear if these second iterations are meant to distinguish some specific type of sample from the first iteration. The metes and bounds of the claims are unclear.

Claim Rejections - 35 USC § 112 – Written Description

3. Claims 1-8 and 11-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The claims have been amended to recite a comparison step with a subject not having or at risk of having a cell proliferative disorder of the breast tissue. The response asserts that para 0051-0069 provide support for the amendment as well as the entire specification, however such

sections do not appear to teach such a comparison step. Any response to this rejection should include specific paragraph (or page) and line number support for the claim amendments.

Claim Rejections - 35 USC § 112 - Enablement

4. Claims 1-8 and 11-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims encompass methods of providing a characterization of a cell proliferative disorder of the breast, a prognosis, a disease free survival, and the probability of response of a subject to one or more treatment regimens by determining the methylation status of PTIX2 or its regulatory region.

The claims broadly encompass treatments that include, but are not limited to estrogen receptor modulators, estrogen receptor down-regulators, aromatase inhibitors, ovarian ablation, LHRH analogues and other centrally acting drugs influencing estrogen production. Accordingly, the claims encompass determining responsiveness to a very wide range of drugs (antisense drugs, ribozymes, antibody therapy, organic and inorganic compounds), which differ in their structure and mechanism of action.

The claims further encompass a significantly broad genus of disorders, including benign and malignant disorders and specifically including ductal carcinoma in situ, lobular carcinoma, colloid carcinoma, tubular carcinoma, medullary carcinoma, metaplastic carcinoma, intraductal carcinoma in situ, lobular carcinoma in situ and papillary carcinoma in situ. These disorders differ with respect to their symptoms and etiology. The claims also include the analysis of subjects that are estrogen or progesterone receptor positive and negative.

The claims include analyzing any sequence in the PITX2 gene which encompasses tens of thousands of nucleotides, for the methylation status of one or more CpG dinucleotides. Additionally, the claims do not set forth how the results of determining the DNA methylation status of the PITX2 genes are used to characterize, prognose, determine disease free survival or responsiveness to therapy for cell proliferative disorder of the breast, and therefore encompass such phenotypic determinations based on either the presence or absence of methylation at any one or more CpG dinucleotides or based on either hypermethylation or hypomethylation of any one or more CpG dinucleotides in the PITX2 genes.

The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

The amount of direction or guidance and Presence and absence of working examples:

The specification teaches a study in which disease-free survival and metastasis-free survival was studied regarding the methylation status of the promoter region of the PITX2 gene in node-negative, estrogen receptor positive human breast carcinoma patients treated with tamoxifen. These findings are limited to an analysis of breast tissue samples and the PITX2 promoter region. Newly amended drawings indicate that a decrease in PITX2 methylation is found in patients with longer disease free survival.

No working examples are provided in which outcome of non-tamoxifen therapy is predicted based on PITX2 methylation status.

No working examples are provided in which a characterization, prognosis, disease free survival, or response to estrogen therapy is predicted for cell proliferative disorders of the breast other than node-negative, estrogen receptor positive breast carcinomas.

The state of the prior art and the predictability or unpredictability of the art:

While methylation status is known to effect gene expression, there is no per se art recognized association between methylation status and response to any estrogen related therapy for any breast tissue cell proliferative disorder. The predictability of correlating methylation status to the various claimed phenotypes is affected by such factors as the identity of CpG

dinucletoides analyzed as well as the type of sample used. In particular, the unpredictability of predicting responsiveness to therapy by assaying for PITX2 methylation at any CpG dinucleotide, as well as the unpredictability of extrapolating the results from one type of therapy to another type of therapy, are corroborated by the teachings in the following art, which includes applicants own work. .

Martens (Martens et al; Cancer Research. 2005. 65(10): 4101-4107) teaches the results of a study of the methylation status of 117 genes, including the PITX2 gene, in 200 steroid hormone receptor responsive tumors in patients who received tamoxifen as first-line treatment for recurrent breast cancer. Martens did not observe an association between methylation status of PITX2 and response to treatment(see Supplemental Tables 1 and 2). Martens (page 4101, col. 2) teaches that "(f)rom a biological point of view, however, first-line single agent endocrine therapy in patients with recurrent breast cancer is an excellent setting to study response to therapy because it is less subject to prognostic influences unavoidably present when a similar study would be done in the adjuvant setting." In discussing the variation in results reported therein as compared to those of Widschwendter, Martens (page 4106, col. 1) states that the "reasons for the differences between that study and ours could be manifold including differences in study design (adjuvant versus first-line treatment), in the CpG sites analyzed, in the technology used, or in size or composition of the tissue collections used. Due to the heterogeneity of the cohorts and the likely confounding influence of steroid hormone receptor status, and different treatment modalities, the results of the study of Widschwendter et al are difficult to interpret." Thus, Martens teaches that while it is possible that there may be a difference in results between adjuvant therapy and first line therapy, it is equally possible that any differences in results may

be due to a number of other factors including the identity of the CpG sites analyzed, the tissue sample analyzed and the steroid receptor status of the breast cancer analyzed. With regard to the teachings of Martens, Nimmrich (Nimmrich et al; Breast Cancer Research and Treatment. 2008. 111:429-437) teaches that "earlier work from our group in clinical specimens did not find PITX2 DNA-methylation to be associated with intrinsic tamoxifen resistance in metastatic breast cancer" (page 430). At page 434, Nimmrich teaches that in the previous retrospective study of Martens, "we did not find DNA-methylation of PITX2 of the primary tumor to be associated with tamoxifen response (given as a first-line single endocrine agent) in metastatic breast cancer. Nimmrich studied DNA-methylation of the PITX2 gene in untreated lymph node-negative hormone receptor positive breast cancer patients. The authors found that hypermethylation of PITX2 was associated with a poor prognosis and disease progression in these patients. Nimmrich also clarifies the distinction between a marker that is prognostic and markers that are predictive of response to treatment, stating that "a prognostic factor is not necessarily also a predictive marker, or vice versa" (page 434). Nimmrich also acknowledges that differences in methylation results may occur between early stage and advanced breast cancer due to the differences in tumor biology (page 434). The teachings of Nimmrich support the unpredictability of extrapolating the results obtained with one type of breast tissue proliferative disorder to other types of breast tissue proliferative disorders (e.g., early stage breast cancer as compared to late stage, metastatic breast cancer), and with one type of therapy to other types of therapy (e.g., primary treatment with tamoxifen as compared to adjuvant treatment of recurrent cancer with tamoxifen).

The claims further broadly encompass methods in which any sample type such as serum/plasma, urine, brain tissue, saliva, is analyzed for the methylation status of CpGs.

However, it is relevant to point out that it is well accepted in the art that gene expression and methylation patterns may vary significantly between tissue. For example, Van Criekinge (PGPUB 2009/0215709; para [0009]) teaches that "Genes that are hypermethylated in tumor cells are strongly specific to the tissue of origin of the tumor." However, the specification does not teach the methylation pattern of the PITX2 gene in blood samples, spinal cord, lymphatic fluid, urine, feces, or tears etc from patients having a breast tissue proliferative disorder. Accordingly, it is highly unpredictable as to whether the results obtained in one sample type, such as primary breast tissue, can be extrapolated to other tissue types.

It is further unpredictable as to whether any single CpG or any combination of any CpGs in any region of the PITX2 gene can be analyzed for the methylation status as indicative of the broadly claimed phenotypes. The claims do not require any type of comparison step with a control, non-cancer or non-responsive sample, and thereby include methods in which the presence or absence of methylation at a single CpG is detected as predictive of any of the broadly claimed phenotypes. However, the specification has not established such an association between any single CpG and characterization, disease free survival, prognosis or response to any treatment. Further, the results in the specification appear to be limited to the regions cited above which consist of portions of the promoter region of the PITX2. It is well known in the art that different regions of a gene may be methylated in cancer tissues and in normal tissues, such that the occurrence of any one methylated CpG alone is not necessarily predictive of phenotype, let alone, characterization, disease free survival, prognosis or response to any treatment of a cell proliferative disorder of the breast tissue. The effect of methylation may vary depending on the location of the methylated CpG. For example, methylation of CpGs present in the promoter

region of a gene may alter gene expression, whereas methylation of CpGs in coding sequences of a gene may not. Regarding the unpredictability of applying methylation results to the prediction of a phenotype, it is relevant to poin out that Ushijima (Nature Reviews. 2005. 5: 223-231) teaches that "interpretation of differential methylation has proven difficult because the significance of methylation alterations depends on the genomic region, and functions of the CpG islands at specific sites have not been fully clarified" (see abstract). Ushijima teaches that both hypermethylation and hypomethylation are associated with the occurrence of cancer (page 223). Ushijima (page 223) also teaches that "it has become recognized that methylation in cancer cells frequently occurs in CGIs outside promoter regions, which do not repress gene transcription, and also in promoter CGIs of genes that cannot be regarded as tumour-suppressor genes. Even in normal cells, methylation of specific CGIs frequently occurs. Therefore, to identify novel tumour suppressor genes silenced in cancer cells by CGI methylation it is necessary to carefully select the particular CGIs to be included in the analysis."

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

While methylation status is known to effect gene expression, there is no per se art recognized association between methylation status and response to any estrogen related therapy for any breast tissue cell proliferative disorder. The predictability of correlating methylation

status to the various claimed phenotypes is affected by such factors as the identity of CpG dinucletoides analyzed as well as the type of sample used.

Although the specification teaches a study in which disease-free survival and metastasis-free survival was studied regarding the methylation status of the promoter region of the PITX2 gene in node-negative, estrogen receptor positive human breast carcinoma patients treated with tamoxifen, this study was limited to an analysis of breast tissue samples and the PITX2 promoter region. However, the art cited above is illustrative of the unpredictable nature of the invention, having found no correlation between prognosis and PITX2 methylation. The skilled artisan would be required to perform extensive trial and error experimentation to determine if a characterization, prognosis, disease free survival, or response to any type of therapy is possible in based on PITX2 methylation status of any portion of the PITX2, as well as for cell proliferative disorders of the breast other than node-negative, estrogen receptor positive breast carcinomas.

There is no specific guidance provided in the specification as to the types of cells or tissues, other than primary breast tissue, which one would be expected to show a change in methylation status in subjects having breast cancer. The specification does not provide sufficient teaching for one of skill in the art to determine which of the thousands of particular CpGs in the PITX2 gene are to be analyzed as predictive of the claimed phenotypes, including response to therapy or prognosis of breast proliferative disorders. The claims encompass methods in which any single CpG or any combination of CpGs in any coding or non-coding region of the PITX2 gene is analyzed for methylation status such that a characterization, prognosis or prediction of outcome of estrogen related therapy is "provided". The claims include analyzing any coding or

non-coding sequence of the PITX2 gene and it's regulatory region for methylation status. However, it appears that the specification analyzed only a region of the promoter for methylation status. Insufficient guidance is provided as to which regions outside of the assayed promoter regions could be analyzed to determine if an increase or decrease level of methylation is correlated with the claimed phenotypes let alone prognosis or estrogen therapy outcome. Additionally, extensive experimentation would be required to identify additional therapies in which PITX2 methylation is correlated with the claimed phenotypes. While methods for determining CpG methylation status are known in the art, such methods provide only the general guidelines that allow researchers to randomly determine if particular CpGs or regions of a gene containing CpGs are methylated. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment.

Given the art accepted unpredictability in the associated field, the experimentation would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

The response traverses the rejection and cites different portions of the specification as provided support for the claimed subject matter. The specification and the newly filed drawings

have been thoroughly reviewed. While the specification and drawing indicate that for node-negative, estrogen receptor positive human breast carcinoma patients treated with tamoxifen, analysis of breast tissue samples and the PITX2 promoter region indicate that a decrease in PITX2 methylation is found in patients with longer disease free survival, the art cited above appears to teach that no association was found between PITX2 methylation status and prognosis following treatment. Additionally, the claims are more broadly drawn as recited above and given the unpredictability in the associated technology, do not bear reasonable scope to the teachings of the specification. Additionally, the response cites several references as indicative of enablement, however it is noted that the reference have not been provided in declaration format. The reason for requiring evidence in declaration or affidavit form is to obtain the assurances that any statements or representations made are correct as provided by 35 U.S.C. 25 and 18, U.S.C. 1001. In Ex parte Gray (10 USPQ2d 1923) the Courts held that conclusory statements made in publications could not substitute for a declaratory evidence filed under 37 CFR 1.132. Furthermore, in Ex parte Ishizaka (BdPatApp&Int 24 USPQ2d 1621), the Courts stated that 37 CFR 1.132 does not recognize the use of a publication as a substitute for a declaration. Consequently, a Declaration filed under 37 CFR 1.132 sworn by at least one of the instant inventors which cites/explains the relevant parts of the references is needed, however applicants should note the timeliness for providing evidence in issues that were raised in a non final office action. As stated in the MPEP: 716.01 [R-2]

(A) Timeliness:
Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:
(1) prior to a final rejection,
(2) before appeal in an application not having a final rejection, or

(3) after final rejection and submitted
(i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or
(ii) with a satisfactory showing under 37 CFR 1.116(b) or 37 CFR 1.195, or
(iii) under 37 CFR 1.129(a).

Applicant is also reminded that nexus is required between the teachings of the specification and any evidence provided in the declaration as well as the claimed invention. For example, it is noted that the references are directed to tamoxifen treatment in certain types of breast cancers, whereas the claims are broader.

Conclusion

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

6. No claims are allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner is a hoteling examiner and can normally be reached Mondays, Tuesdays, and Thursdays from 8:00 AM to 2:00 PM, and Fridays from 8:00 AM to 12:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen, can be reached on (571) 272-0731. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Jehanne Sitton/
Primary Examiner
Art Unit 1634